Cancer Cell
Obituary

Tony Pawson (1952–2013)

Tony Pawson, a world-renowned scientist and a pioneer who made groundbreaking contributions that shaped our current understanding of how cellular signal transduction pathways are regulated in normal tissues and in cancer cells, sadly passed away on August 7, 2013 at the age of 60.

Anthony James Pawson was born on October 18, 1952 in Maidstone in the County of Kent in England. His mother was a high school biology teacher with a special interest in botany. His father was a well-known soccer player who played for the Oxford University team and for the English soccer team at the 1952 Olympiad in Helsinki. His father was also a successful cricket player, a member of the English fly-fishing team for the 1989 world championship, and, later in life, an author and correspondent for the Observer. Tony mentioned that he obtained his interest in science and the natural world from his mother, but his passion for writing, his competitiveness, his determination, and his own love of fly fishing from his father.

After spending his school years at Winchester College, Tony received his undergraduate education as a member of Clare College at Cambridge University. In Cambridge, he became interested in biochemistry and had the opportunity to spend time in the laboratory performing experiments in the field of protein synthesis. In 1973, Tony moved to London for his Ph.D. degree at ICRF (Imperial Cancer Research Fund, which is now called Cancer Research UK) with Alan Smith. During Tony's Ph.D. studies, the focus of his research was the mode of action and mechanism of oncogenesis mediated by retroviruses and how retroviruses propagate themselves. After obtaining his Ph.D. in 1976, Tony crossed the Atlantic and worked at the laboratory of Steven Martin at the University of California, Berkeley. Martin focused on investigating the mechanism of action of Rous Sarcoma virus, a retrovirus that causes tumors in chickens and transforms cultured cells by expressing its oncogenic protein, v-Src. During his postdoctoral training, Tony started to explore the structure and mechanism of action of the Fujinami avian sarcoma virus and the role played by its oncogenic protein, v-Fps, in cell transformation. In 1981, Tony took an independent faculty position at the University of British Columbia in Vancouver, where he continued to investigate the oncogenic v-Fps protein, increasingly focused on the role of its tyrosine kinase activity in cell transformation. A few years later, in 1985, Tony moved to the Samuel Lunenfeld Research Institute at Toronto's Mount Sinai Hospital, where he became Distinguished Investigator and Director of Research, and was also Professor of Molecular Genetics at the University of Toronto. Tony remained in Toronto for the rest of his career.

Tony was very much at the center of an exceptional convergence of several different areas of basic biomedical research during the last three decades of the 20th century, which revolutionized our understanding of the molecular basis of cell signaling and malignant transformation. These important discoveries contributed to new approaches for the development of many new cancer drugs.

Tony Pawson

The molecular basis of cancer was revealed through a stunning explosion of discoveries. These advances include: the genetic origins of malignancies; the mode of action of retroviral oncogenes; the discoveries of new growth factors and cytokines that stimulate cell proliferation, differentiation, and other vital cellular processes; the methodology to identify and track genetic changes in cancer cells; the identification of evolutionary conserved critical components of cellular signaling pathways in nematodes and *Drosophila*; and biochemical determination of how signals that are initiated at the cell surface and are propagated intracellularly by growth factor receptor activation stimulate cell proliferation and other basic processes that are required for cellular homeostasis. Subsequent application of this new knowledge led to the development of what is now defined as cancer-targeted therapies, which have changed the way in which many deadly cancers are now being treated.

Tony is perhaps best known for his identification of the Src homology 2, or SH2, domain and the resulting concept of modular interaction domains as key elements of the molecular infrastructure of signaling. While inspecting the primary structure of v-Fps early in his career, Tony and his colleagues made an important observation. They realized that, in addition to the catalytic tyrosine kinase domain of v-Fps that is also seen in the oncogenic Src and Abl tyrosine kinases, these oncogenic proteins contain a conserved noncatalytic region of ~100 amino acids, which they termed the SH2 domain (the tyrosine kinase is the SH1 domain). Through biochemical analyses of the tyrosine kinase activities of a variety of v-Fps mutants and comparison of their cellular transformation properties, Tony's laboratory demonstrated that the v-Fps SH2 domain plays an important role in controlling both the tyrosine kinase activity and cell transformation. Members of the Src and Abl tyrosine kinase families contain an additional conserved noncatalytic region of ~60 amino acids, designated the Src homology 3 (SH3) domain,

located N terminal to the SH2 domain of Src and Abl. Tony proposed that SH2 and SH3 domains function as independent protein modules that maintain their unique functions in different host proteins and that they play important regulatory roles in controlling the activity and localization of Src and other cytoplasmic tyrosine kinases. This concept of modularity gained significant traction when the laboratory of Hidesaburo Hanafusa found that the transforming gene of the CT10 retrovirus, v-Crk, encodes a viral gag protein fused to only SH2 and SH3 domains, demonstrating that SH2 and SH3 domains can function alone as oncogenes. The SH2 domain of Crk was shown to bind directly to phosphotyrosine (P-Tyr)-containing proteins, indicating that SH2 domains may recognize specific tyrosine-containing regions in a phosphorylation-dependent manner. Because many signaling molecules with different enzymatic activities, such as phospholipase Cγ (PLCγ), Ras GTPase-activating protein (GAP), and the Src family kinases, contain SH2 domains, this realization provided a link between activation of cytoplasmic and receptor tyrosine kinases (RTKs). Indeed, experiments performed in Tony's and other laboratories demonstrated that, following their stimulation with ligands, the EGF receptor (EGFR), PDGF receptor (PDGFR), and other activated RTKs form physical complexes with signaling molecules such as PLCγ, GAP, or adaptor proteins such as Grb2 or Nck by binding to the SH2 domains of these signaling proteins. For example, in 1992, Tony's laboratory demonstrated that complex formation between the scaffold protein Shc and phosphotyrosines on activated EGFR leads to tyrosine phosphorylation of Shc, which in turn forms a complex with the SH2 domain of the adaptor protein Grb2. Grb2 uses its two SH3 domains to bind the guanine nucleotide exchange factor Sos so that Shc effectively recruits Sos to the cell membrane (and thus activates Ras) through SH2 and SH3 domain-mediated interactions. The resulting activated (GTP-bound) Ras molecules stimulate a cascade of three protein kinases, resulting in activation and nuclear translocation of MAP kinase. This highly conserved signaling pathway relays information from the cell membrane to the nucleus and other intracellular compartments to regulate a variety of EGF-induced cellular processes.

More than 20 years later, in one of his last and most elegant articles that was published in July 2013—only three weeks before he passed away—Tony's laboratory described a comprehensive analysis of the cellular functions of Shc at different time points following EGF stimulation. His laboratory used mass spectrometry and other state-of-the-art technologies to demonstrate that Shc responds to EGF stimulation in "multiple waves of distinct phosphorylation events and protein interactions." In other words, at different time points following EGF stimulation, Shc forms distinct complexes with different positive or negative regulators to control many of the pleiotropic cellular responses induced by EGF stimulation. These two publications, spanning more than two decades of scientific effort, provide a clear testament to the originality, brilliance, and focus that have been a hallmark of Tony's entire scientific career.

In addition to his main interest in elucidating the biological roles and mechanisms underlying the actions of SH2, SH3, and other small protein modules in mediating protein-protein and other interactions during signal transduction, Tony's laboratory made important contributions to other fields of biomedical research, including analysis of molecular mechanisms that govern cellular polarity and molecular mechanisms that control axon guidance, as well as systems biology with an emphasis on elucidation of the dynamic nature of molecular events during cellular signaling. In all of these studies, he showed an uncanny ability to marry advances in technology with the most important biological questions to view the entire cell in terms of its molecular infrastructure.

The death of Tony Pawson shocked and saddened his many colleagues, former students, postdoctoral fellows, and friends all over the world. We will miss Tony's thoughtful and eloquent lectures. We will miss Tony's inspiring publications and the elegance and clarity of his scientific mind. We will miss our informal discussions at scientific meetings that were filled with good humor, Tony's characteristic chuckle, and his sharp insights. Tony's legacy will be remembered and will be an inspiration for future generations of scientists.

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